0011499339 BIOSIS NO.: 199800293586
Structure function analysis of the actin ADP-ribosylating Clostridium botulinum C2 toxin
AUTHOR: Barth H; Preiss J; Roebling R; Hofmann F; Just I; Aktories K
AUTHOR ADDRESS: Inst. Pharmakol. Toxikol., Albert-Ludwigs-Univ. Freiburg, D-79104 Freiburg, Germany**Germany
JOURNAL: Naunyn-Schmiedeberg's Archives of Pharmacology 357 (4 SUPPL): p R60 1998 1998
MEDIUM: print
CONFERENCE/MEETING: 39th Spring Meeting of the German Society for Experimental and Clinical Pharmacology and Toxicology Mainz, Germany March 17-19, 1998; 19980317
SPONSOR: German Society for Experimental and Clinical Pharmacology and Toxicology
ISSN: 0028-1298
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English
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0010047850 BIOSIS NO.: 199598515683
Mutations in the elongation factor 2 gene which confer resistance to diphtheria toxin and Pseudomonas exotoxin A: Genetic and biochemical analyses
AUTHOR: Foley Brian T; Moehring Joan M; Moehring Thomas J (Reprint)
AUTHOR ADDRESS: 316 Stafford Hall, Univ. Vermont, Burlington, VT 05405, USA **USA
JOURNAL: Journal of Biological Chemistry 270 (39): p23218-23225 1995
1995
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Both diphtheria toxin and Pseudomonas exotoxin A inhibit eukaryotic protein synthesis by **ADP**-ribosylating diphthamide, a posttranslationally modified histidine residue present in the elongation factor 2 (EF-2) protein. Elongation factor 2 cannot be **ADP**-ribosylated by the toxins unless this histidine is modified. In this report we identify three new point mutations in toxin-resistant alleles of the Chinese hamster ovary cell elongation factor 2 gene. The mutations resulted in amino acid substitutions at positions 584 (serine to glycine), 714 (isoleucine to asparagine), and 719 (glycine to aspartic acid). All three amino acid substitutions prevented the biosynthesis of diphthamide. The amount by which the toxins reduced protein synthesis in each of these mutant cell strains suggested that all three mutations also either impaired the function of EF-2 or reduced its steady state level in the cytoplasm. Western blot analysis showed that equal amounts of EF-2 were present in each of the cell strains, indicating that the mutations impaired the catalytic function of EF-2.

3855885 Genuine Article#: QL639 Number of References: 67
Title: STRUCTURE AND FUNCTION OF **CLOSTRIDIUM**-BOTULINUM TOXINS
Author(s): OGUMA K; FUJINAGA Y; INOUE K
Corporate Source: OKAYAMA UNIV,SCH MED,DEPT BACTERIOL,2-5-1 SHIKATA CHO/OKAYAMA 700//JAPAN/
Journal: MICROBIOLOGY AND IMMUNOLOGY, **1995**, V39, N3, P161-168
ISSN: 0385-5600
Language: ENGLISH Document Type: **REVIEW**

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04022001 Genuine Article#: QZ347 Number of References: 140
Title: MOLECULAR ASPECTS OF TETANUS AND BOTULINUM **NEUROTOXIN** POISONING
Author(s): AHNERTHILGER G; BIGALKE H
Corporate Source: FREE UNIV BERLIN,KLINIKUM BENJAMIN FRANKLIN,MEDKLIN & POLIKLIN,GASTROENTEROL ABT/W-1000 BERLIN//GERMANY/; HANNOVER MED SCH,INST TOXIKOL/HANNOVER//GERMANY/
Journal: PROGRESS IN NEUROBIOLOGY, **1995**, V46, N1 (MAY), P83-96
ISSN: 0301-0082
Language: ENGLISH Document Type: **REVIEW**
Abstract: **Clostridial** neurotoxins, tetanus and the botulinum toxins A-G, are high molecular weight proteins consisting of a heavy chain which is responsible for the internalisation and a light chain possessing a zinc-dependent proteolytic activity. They exclusively proteolyse either the vesicle membrane protein, synaptobrevin or two integral plasma membrane proteins, SNAP 25 and syntaxin. Together with cytosolic proteins these proteins form the SNARE complex involved in vesicle exocytosis, and their cleavage blocks the latter process. **Clostridial** neurotoxins have now become powerful tools to investigate the final events occurring during secretion in neuronal, endocrine, and non-neuronal cells. They are applied to dissect the specific interactions of the SNARE protein complex with cytosolic fusogens and other modulators of exocytosis. Whereas exocytosis is not essential for the survival of cells, the organism as a whole will fall victim to a few nanograms since interneuronal and neuromuscular transmission is vital to muscular control, especially in respiration. Although all **clostridial** neurotoxins by their light chains attack proteins of the SNARE complex, tetanus **toxin** and the various botulinum toxins differ dramatically in their clinical symptoms. The biological information for this difference resides on the respective heavy chains which select different transport routes carrying the light chain from the place of entrance to the final compartment of action, So far the different transport vesicles used either by the various botulinum neurotoxins or by tetanus **toxin** are not yet defined. Nevertheless at least one of the botulinum toxins serves as a beneficial drug in the treatment of severe neuromuscular spasms.

Snake protein compare

03320862 Genuine Article#: NV897 Number of References: 105
Title: MECHANISM OF ACTION OF TETANUS AND BOTULINUM NEUROTOXINS
Author(s): MONTECUCCO C; SCHIAVO G
Corporate Source: UNIV PADUA,CNR,CTR BIOMEMBRANE,VIA TRIESTE 75/I-35121 PADUA//ITALY/; UNIV PADUA,DIPARTIMENTO SCI BIOMED/I-35121 PADUA//ITALY/
Journal: MOLECULAR MICROBIOLOGY, **1994**, V13, N1 (JUL), P1-8
ISSN: 0950-382X
Language: ENGLISH Document Type: **REVIEW**
Abstract: The **clostridial** neurotoxins responsible for tetanus and botulism are metallo-proteases that enter nerve cells and block neurotransmitter release via zinc-dependent cleavage of protein components of the neuroexocytosis apparatus. Tetanus **neurotoxin** (TeNT) binds to the presynaptic membrane of the neuromuscular junction and is internalized and transported retroaxonally to the spinal cord. Whilst TeNT causes spastic paralysis by acting on the spinal inhibitory interneurons, the seven serotypes of botulinum neurotoxins (BoNT) induce a flaccid paralysis because they intoxicate the neuromuscular junction. TeNT and BoNT serotypes B, D, F and G specifically cleave VAMP/synaptobrevin, a membrane protein of small synaptic vesicles, at different single peptide bonds. Proteins of the presynaptic membrane are specifically attacked by the other BoNTs: serotypes A and E cleave SNAP-25 at two different sites located within the carboxyl terminus, whereas the specific target of serotype C is syntaxin.

Review articles - PMH

24/7/20 (Item 20 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

00435178 Genuine Article#: DR725 Number of References: 100
Title: **CLOSTRIDIAL** ADP-RIBOSYLTRANSFERASES - MODIFICATION OF LOW-MOLECULAR-WEIGHT GTP-BINDING PROTEINS AND OF ACTIN BY **CLOSTRIDIAL** TOXINS
Author(s): AKTORIES K
Corporate Source: UNIV ESSEN KLINIKUM,INST PHARMAKOL,HUFELANDSTR 55/D-4300 ESSEN//FED REP GER/
Journal: MEDICAL MICROBIOLOGY AND IMMUNOLOGY, **1990**, V179, N3, P 123-136
Language: ENGLISH Document Type: **REVIEW**

6281301 Genuine Article#: YG152 Number of References: 225
Title: Pharmacologic characterization of botulinum **toxin** for basic science and medicine
Author(s): Pearce LB (REPRINT) ; First ER; MacCallum RD; Gupta A
Corporate Source: ASSOCIATED SYNAPSE BIOL,11 HURLEY ST/CAMBRIDGE//MA/02141 (REPRINT); BOSTON UNIV,SCH MED, DEPT PHARMACOL & EXPT THERAPEUT/BOSTON//MA/02118
Journal: TOXICON, **1997**, V35, N9 (SEP), P1373-1412
ISSN: 0041-0101 Publication date: 19970900
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB
Language: English Document Type: **REVIEW**
Abstract: The use of Botulinum **neurotoxin** (BoNT) is increasing in both clinical and basic science. Clinically, intramuscular injection of nanogram quantities of BoNT is fast becoming the treatment of choice for a spectrum of disorders including movement disorders such as torticollis, blepharospasm, Meige Disease, and hemifacial spasm (Borodic er al., 1991, 1994a; Jankovic and Brin, 1991; Clarke, 1992). Neuroscientists are using BoNTs as tools to develop a better understanding of the mechanisms underlying the neurotransmitter release process, Consequently, our ability to accurately and reliably quantify the biologic activity of botulinum **toxin** has become more important than ever. The accurate measurement of the pharmacologic activity of BoNTs has become somewhat problematic with the most significant problems occurring with the clinical use of the toxins, The biologic activity of BoNTs has been measured using a variety of techniques including assessment of whole animal responses to in vitro effects on neurotransmitter release. The purpose of this review is to examine the approaches employed to characterize, quantify and investigate the actions of the BoNTs and to provide a guide to aid investigators in determining which of these methods is most appropriate for their particular application or use. (C) 1997 Elsevier Science Ltd.

06507052 Genuine Article#: YX893 Number of References: 64
Title: Phylogeny and taxonomy of the food-borne pathogen **Clostridium** botulinum and its neurotoxins
Author(s): Collins MD (REPRINT) ; East AK
Corporate Source: BBSRC,INST FOOD RES, DEPT MICROBIOL, EARLEY GATE, WHITEKNIGHTS RD/READING RG6 6BZ/BERKS/ENGLAND/ (REPRINT)
Journal: JOURNAL OF APPLIED MICROBIOLOGY, **1998**, V84, N1 (JAN), P5-17
ISSN: 1364-5072 Publication date: 19980100
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD, OXON, ENGLAND OX2 0NE
Language: English Document Type: **REVIEW**

Review article

00781815 1998015655
Bacterial metalloprotease as the toxic factor in infection
Miyoshi S.i.; Shinoda S.
ADDRESS: S.i. Miyoshi, Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama 700, Japan
Journal: Journal of Toxicology - Toxin Reviews, 16/4 (177-194), **1997**
, United States
PUBLICATION DATE: 19970000
CODEN: JTTRD
ISSN: 0731-3837
DOCUMENT TYPE: **Review**
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 70

Metalloproteases, in which zinc metal ion is essential for catalytic activity, are produced by various human pathogenic bacteria. These metalloproteases have the consensus sequence HEXXH, in which two histidine residues function as the first and second zinc ligands. However, on the basis of the location of the third zinc ligand, they are classified into three families: the thermolysin, serralysin and **neurotoxin** families. Members of the thermolysin family are synthesized as an inactive precursor with a N-terminal propeptide, and maturation of the precursor is achieved by several processing stages. The metalloprotease in the serralysin family is generated without a conventional propeptide, and its transport is supported by additional secreted proteins. A wide variety of pathological actions of bacterial metalloproteases have been documented. In local bacterial infections, such as keratitis, dermatitis and pneumonia, the metalloprotease functions as a decisive virulence determinant. The protease generated at the site of the infection causes necrotic or hemorrhagic tissue damage through digestion of structural components of the ground substance. The protease also enhances vascular permeability and forms edematous lesions through generation of the inflammatory mediators, histamine and bradykinin. Additionally, permeability enhancement and/or tissue damage allows bacterial dissemination into the systemic circulation. In systemic infections such as septicemia, the metalloprotease acts as a synergistic virulence factor. The disordered proteolysis of many plasma

Review article.

01196387 Genuine Article#: GD367 Number of References: 90
Title: CELLULAR AND MOLECULAR ACTIONS OF BINARY TOXINS POSSESSING ADP-RIBOSYLTRANSFERASE ACTIVITY
Author(s): CONSIDINE RV; SIMPSON LL
Corporate Source: THOMAS JEFFERSON UNIV,JEFFERSON MED COLL,DEPT PHYSIOL/PHILADELPHIA//PA/19107; THOMAS JEFFERSON UNIV,JEFFERSON MED COLL,DEPT MED & PHARMACOL/PHILADELPHIA//PA/19107
Journal: TOXICON, **1991**, V29, N8, P913-936
Language: ENGLISH Document Type: **REVIEW**
Abstract: **Clostridial** organisms produce a number of binary toxins. Thus far, three complete toxins (botulinum, perfringens and spiroforme) and one incomplete **toxin** (difficile) have been identified. In the case of complete toxins, there is a heavy chain component (M(r) approximately 100,000) that binds to target cells and helps create a docking site for the light chain component (M(r) approximately 50,000). The latter is an enzyme that possesses mono(ADP-ribosyl)transferase activity. The toxins appear to proceed through a three step sequence to exert their effects, including a binding step, an internalization step and an intracellular poisoning step. The substrate for the toxins is G-actin. By virtue of ADP-ribosylating monomeric actin, the toxins prevent polymerization as well as promoting depolymerization. The most characteristic cellular effect of the toxins is alteration of the cytoskeleton, which leads directly to changes in cellular morphology and indirectly to changes in cell function (e.g. release of chemical mediators). Binary toxins capable of modifying actin are likely to be useful tools in the study of cell biology.

0014981851 BIOSIS NO.: 200400352640
Synaptotagmins I and II act as nerve cell receptors for botulinum **neurotoxin** G
AUTHOR: Rummel Andreas; Karnath Tino; Henke Tina; Bigalke Hans; Binz Thomas (Reprint)
AUTHOR ADDRESS: Inst Biochem, Med Hsch Hannover, D-30625, Hannover, Germany **Germany
AUTHOR E-MAIL ADDRESS: Binz.Thomas@mh-hannover.de
JOURNAL: Journal of Biological Chemistry 279 (29): p30865-30870, 30856 July 16, 2004 2004
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Botulinum neurotoxins (BoNTs) induce muscle paralysis by selectively entering cholinergic motoneurons and subsequent specific cleavage of core components of the vesicular fusion machinery. Complex gangliosides are requisite for efficient binding to neuronal cells, but protein receptors are critical for internalization. Recent work evidenced that synaptotagmins I and II can **function** as protein receptors for BoNT/B (Dong, M., Richards, D. A., Goodnough, M. C., Tepp, W. H., Johnson, E. A., and Chapman, E. R. (003) J. Cell Biol. 162, 1293-1303). Here, we report the protein receptor for a second BoNT serotype. Like BoNT/B, BoNT/G employs synaptotagmins I and II to enter phrenic nerve cells. Using pull-down assays we show that only BoNT/G, but neither the five remaining BoNTs nor tetanus **neurotoxin**, interacts with synaptotagmins I and II. In contrast to BoNT/B, interactions with both isoforms are independent of the presence of gangliosides. Peptides derived from the luminal domain of synaptotagmin I and II are capable of blocking the neurotoxicity of BoNT/G in phrenic nerve preparations. Pull-down and neutralization assays further established the membrane-juxtaposed 10 luminal amino acids of synaptotagmins I and II as the critical segment for **neurotoxin** binding. In addition, we show

12967957 Genuine Article#: 838SI Number of References: 72
Title: Large **clostridial** cytotoxins: cellular biology of Rho/Ras-glucosylating toxins
Author(s): Schirmer J; Aktories K (REPRINT)
Corporate Source: Univ Freiburg,Inst Expt Klin Pharmakol & Toxicol,Otto Krayer Haus,Albertstr 25/D-79104 Freiburg//Germany/ (REPRINT); Univ Freiburg,Inst Expt Klin Pharmakol & Toxicol,D-79104 Freiburg//Germany/(Klaus.Aktories@pharmakol.uni-freiburg.de)
Journal: BIOCHIMICA ET BIOPHYSICA ACTA-GENERAL SUBJECTS, 2004, V1673, N1-2 (JUL 6), P66-74
ISSN: 0304-4165 Publication date: 20040706
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: **REVIEW**
Abstract: Mono-O-glycosylation of eukaryotic target proteins is the molecular mechanism of bacterial protein toxins of the family of large **clostridial** cytotoxins. This **toxin** family encompasses several high molecular mass proteins (>250 kDa) of various **Clostridia** species that are implicated in severe human diseases. **Toxin** A and **toxin** B from **Clostridium** difficile are the causative agents of pseudomembraneous colitis and antibiotic-associated diarrhea. Lethal **toxin** and hemorrhagic **toxin** from **Clostridium** sordellii as well as alpha-**toxin** from **Clostridium** novyi are involved in the gas gangrene syndrome. The common mode of action of large **clostridial** cytotoxins is elicited by specific glycosylation of small GTP-binding proteins in the cytosol of target cells using activated nucleotide sugars as cosubstrates. Specific modification at a single threonine residue in the small GTPases renders these important key players of various signaling pathways inactive. This minireview intends to give an overview on structure-function analysis and mode of action of the large **clostridial** cytotoxins, as well as on the resulting functional consequences of glycosylation of target proteins.

Neurotoxins are subtoxins of the toxins that are claimed.